REMARKS

Claim rejection under 35 U.S.C. § 103(a)

Claims 1, 2 and 4-16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Odin et al (CANCER INVESTIGATION, Vol. 16 No. 7, 1998, page 447-455) in view of Lawrence (US Patent 4,931,441)

Odin describes 5,10-methylenetetrahydrofolic acid repeatedly as highly sensitive to oxidation. See, e.g., page 447 and the abstract. Only a rigorous exclusion of atmospheric oxygen by the use of special technical devices for the reconstitution of solid formulations and the injection of 5,10-methylenetetrahydrofolic acid in an air-free environment can make this substance manageable. See, e.g., abstract, teaching the "thorough exclusion of atmospheric O_2" and the use of a "suitable air-occlusive system." This air-free handling is described as being imperative for 5,10-methylenetetrahydrofolic acid. See, e.g., page 545, second column, lines 5-7.

Compositions according to the present invention, however, show a totally different behaviour. The strikingly remarkable difference in stability against the mentioned publication is shown in the attached tabular and graphical form of the data based on examples 2, 3 and 8 of the present application. Example 3 of the present invention in fact contain amongst others a comparison of the stability data of a solution prepared according to the present invention against the data published by Odin et al.

A person skilled in the art would surely not expect the demonstrated behaviour of the claimed substances and there is nothing within Odin that would have lead one of ordinary skill in the art to the claimed compositions. The claims of the present application are therefore have significant highly unexpected attributes/advantages, and inventiveness over the prior art.

US 4,931,441 relates to the stabilization of aqueous solutions containing 5-formyltetrahydrofolic acid by the addition of citrate. US 4,931,441 discloses the use of citrate explicitly and only as a buffer agent (see e.g. column 2 line 13, column 2 lines 25-26, column 2 lines 33-38 and column 2 line 54) as they state that 5-formyltetrahydrofolic acid undergoes hydrolysis at a pH below 7.0, such as in the range of 6.5-7.0 (see column 1 lines 50-52). The preferred pH value as disclosed by US 4,931,441 is 8.1±0.1 (see column 2 line 42, column 2 line 61, column 3 line 3, column 3 line 16, claim 2, claim 6 and claim 10). US 4,931,441 also refers to an upper pH as being "not higher than 8.5" (see column 2 lines 18-19, column 3 line 5, claim 1, claim 5 and claim 11). Compare to newly added claim 19.

Even though not necessary in view of the comments and data above, the following additional comments are provided.

The stabilization of 5-formyltetrahydrofolic acid, particularly solutions thereof, cannot be compared with the stabilization of 5,10-methylenetetrahydrofolic acid solutions. The methylene group in 5,10-methylenetetrahydrofolic acid, which is incorporated in a five-membered ring, results in properties of this substance which differ considerably from those of 5-formyltetrahydrofolic acid. This is manifested, for example, in a significantly different stability behaviour and in different paths of decomposition. So 5-formyltetrahydrofolic acid does not exhibit any dissociation behaviour and is far more stable in pharmaceutically acceptable aqueous solutions, even without the addition of sodium citrate and sodium hydroxide. In contrast 5,10-methylenetetrahydrofolic acid in solution is always in equilibrium with formaldehyde and tetrahydrofolic acid, which is distinguished by its extremely high sensitivity to oxidation. By the current invention this sensitivity of 5,10-methylenetetrahydrofolic acid to oxidation is reduced to a level where the substance becomes manageable and the stability of 5,10-methylenetetrahydrofolic acid is adequate for the preparation of aqueous solutions, suspensions and solid forms such as powders or lyophilisates. Surprisingly, this stabilisation occurs even in the absence of a reducing agent. Thus, even without additions of reducing agents (antioxidants) and without the exclusion of atmospheric oxygen, 5,10-methylenetetrahydrofolic acid solutions are stable for several hours. This is all the more surprising since stable compositions of 5,10-methylenetetrahydrofolic acid cannot be obtained using acetate, oxalate, maleate and salts of other acids instead of citrate. This is also in contrast to the situation for 5-formyltetrahydrofolic acid, where an effect comparable with that of citrate can be obtained with acetate (see e.g. WO 95/26963).

In 5-formyltetrahydrofolic acid solutions citrate may reduce hydrolysis and oxidative cleavage of the basic skeleton and thus reduces the formation of products such as p-aminobenzoylglutamic acid and pterin- and tetrahydropterin derivatives. In contrast to this, for 5,10-methylenetetrahydrofolic acid in the basic pH region citrate inhibits the separation of formaldehyde (hydrolysis) from the molecule. This is a striking and surprising difference in the behaviour of these two compounds, both of which form part of the folate class of substances. So the unexpected stabilisation of 5,10-methylenetetrahydrofolic acid with citrate at basic pH values is due to a surprising synergistic effect of the citrate buffer solution in this pH range. Complex formation between citrate and 5,10-methylenetetrahydrofolic acid on the one hand and between citrate and the counterion (salt) of 5,10-methylenetetrahydrofolic acid on the other hand makes a

decisive contribution to the stabilisation of the methylene group by inhibiting the separation of formaldehyde (hydrolysis) from the 5,10-methylenetetrahydrofolic acid molecule. The formation of tetrahydrofolic acid, which is extremely sensitive to oxidation, is thereby prevented, as is the decomposition of 5,10-methylenetetrahydrofolic acid.

Claim 3 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Odin et al (CANCER INVESTIGATION, Vol. 16 No. 7, 1998, page 447-455) in view of Lawrence (US Patent 4,931,441), further in view of Cobb et al (US Patent 5,989,566).

Cobb does not cure the deficiencies of the primary references. Thus, for at least the reasons discussed above, this claim too should be patentable. Nevertheless, the following comments are provided.

The formaldehyde used in dependent claim 3 takes the role of pushing the equilibrium in between 5,10-methylenetetrahydrofolic acid on the one side and tetrahydrofolic acid together with formaldehyde on the other side into the direction of 5,10-methylenetetrahydrofolic acid. By this formaldehyde as adjuvant additionally supports the inhibition of the separation of formaldehyde (hydrolysis) from the molecule in the basic pH region. This role of formaldehyde is totally different from the role as disclosed by US 5,989,566 using formaldehyde most probably only as biological preservative for the claimed vaccine compositions.

Claim 17 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Odin et al (CANCER INVESTIGATION, Vol. 16 No. 7, 1998, page 447-455) in view of Lawrence (US Patent 4,931,441), further in view of Rabelink et al (US PGUB 2002/0052374) and Binderup (US PGPUB 2002/0183277).

Rabelink and Binderup do not cure the deficiencies of the primary references. Thus, for at least the reasons discussed above, this claim too should be patentable.

New Claims

Support for new claims 21 to 24 can be found in the specification, e.g., on page 3, lines 24-25.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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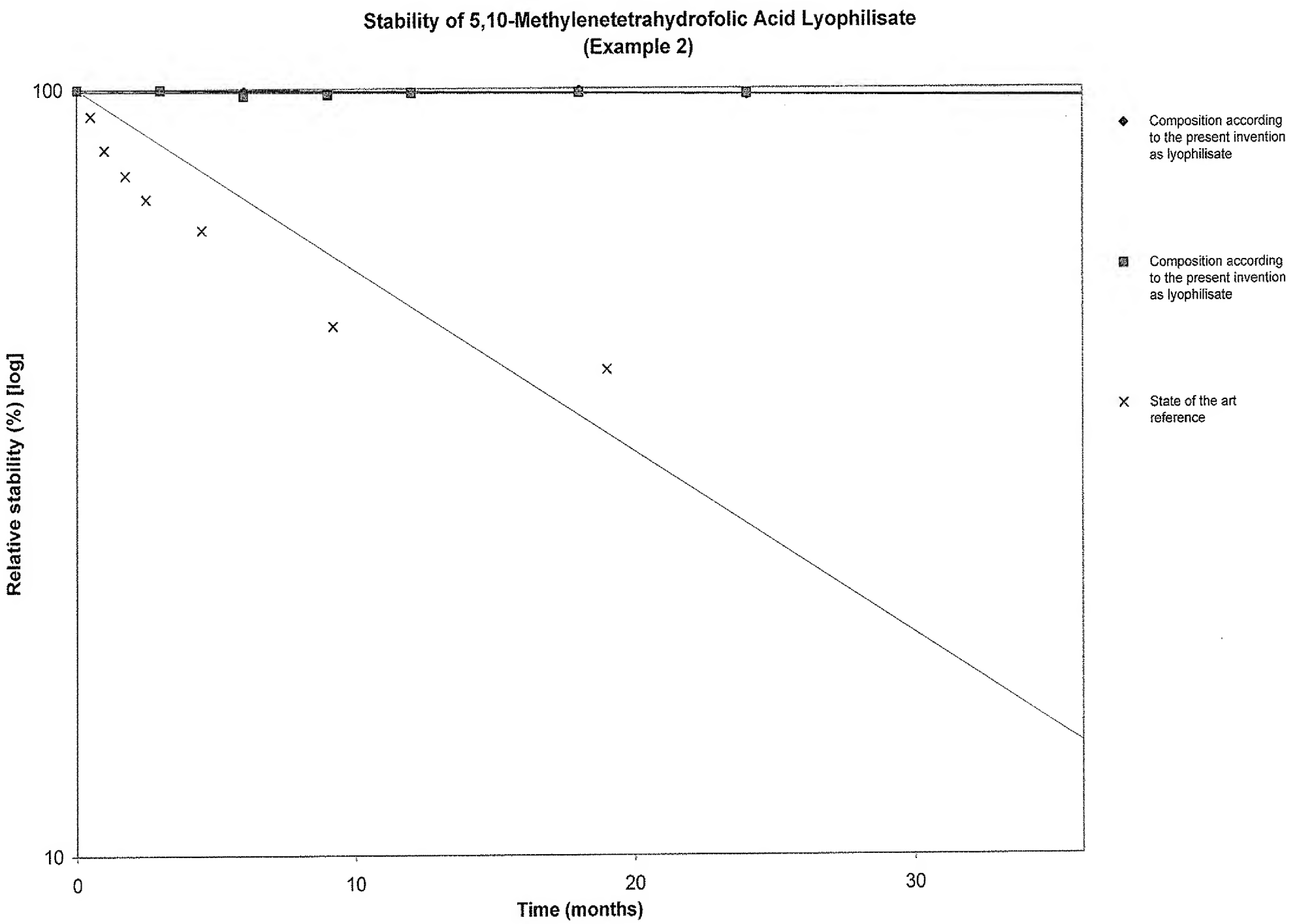
Stability of 5,10-Methylenetetrahydrofolic Acid Lyophilisate, according to Example 2

	Reference	Temperature	Remarks	Example	Relative Stability (Months) 0	0.5	1	1.75	2.5	3	4.5	6	9	9.2	12	18	19	24	36
Composition according to the present invention																			
1	Arn 1466-A	+4°C	Composition according to the present invention as lyophilisate	2	100					100.4		99.3	98.5		99.0	99.4		98.0	
2	ACC0447	-15°C	Composition according to the present invention as lyophilisate	2	100					99.8		97.9	98.3		98.8	98.8		98.4	
State of the art reference																			
B	Co 751	+25°C	State of the art reference	2	100	92.3	83.4	77.2	71.9		65.5			49.1			43.0		


Stability of 5,10-Methylenetetrahydrofolic Acid Lyophilisate
(Example 2)
100
10
Relative stability (%) [log]
0
10
20
30
Time (months)
Composition according to the present invention as lyophilisate
Composition according to the present invention as lyophilisate
State of the art reference

Stability of 5,10-Methylenetetrahydrofolic Acid Solutions at +25°C, according to Examples 3 and 8

	Reference	Temperature	Remarks	Example	Relative Stability (Hours) 0	0.67	1.33	2	2.67	3.33	4	5.33	6	12	24	26	23.2	32.2	48
Composition according to the present invention																			
1	ACC0448	+25°C	Composition according to the present invention as diluted solution in physiological common salt solution, without the exclusion of air	3	100	97.6	95.1	94.6	93.7	92.1	89.9							51.8	
2	ACC0447	+25°C	Composition according to the present invention as diluted aqueous solution, without the exclusion of air	3	100	97.7	97.0	96.6	94.8	93.8	93.3						70.9		
3	ACC0447	+25°C	Composition according to the present invention as concentrated aqueous solution, without the exclusion of air	3	100			100.2			99.2		98.1	95.9	86.2				
4	Am-1758-2/a	+25°C	Composition according to the present invention as concentrated aqueous solution, without the exclusion of air	8	100	100.2	99.1		99.2		98.4	97.7							
State of the art reference																			
B	Odin et. al.	+25°C	State of the art reference in physiological common salt solution, under the exclusion of air exposure	3	100						58.0				38.0	18.0			8.0
C	Odin et. al.	+25°C	State of the art reference in physiological common salt solution, without the exclusion of air	3	100						84.0				12.0	8.0			6.0

Stability of 5,10-Methylenetetrahydrofolic Acid Solutions at +25°C (Examples 3 and 8)